# Small intestinal submucosa-derived extracellular matrix bioscaffold significantly enhances angiogenic factor secretion from human mesenchymal stromal cells.

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**Public Summary:**
Mesenchymal stromal cells (MSCs) are one of the few stem cell types to have reached late stage clinical trials for a variety of indications, including multiple trials as therapeutic agents for ischemic tissue repair. In addition to their multipotent differentiation potential, a strong paracrine effect has been proposed as the principal mechanism that contributes to tissue repair. The MSC treatment for ischemic heart disease (IHD) has proven especially promising, as the pro-angiogenic, pro-survival, and pro-immunomodulatory paracrine signals released by MSCs can rescue the native cells of an injured heart. The stimulation of angiogenesis is of particular importance when treating cardiovascular disease, as it has been shown that improvement in angiogenic support accounts for amelioration of coronary artery disease following bone marrow (BM) cell transplantation. BM-derived MSCs secrete angiogenic factors that are critical for vascular network remodeling. Interleukin (IL)-8, an inflammatory chemokine with potent pro-angiogenic properties, is upregulated in ischemic injuries and has been shown to promote homing of BM-derived cells to sites of injury. Moreover, IL-8 induced VEGF production and that this VEGF production in human BM-derived MSCs significantly increased the in vitro angiogenic response compared with basal-secreted VEGF. In the present study we therefore looked at VEGF and IL-8 secretion from MSCs as they are two key angiogenic factors. The majority of clinical trials using MSCs to treat IHD have used a needle or catheter injection of therapeutic cells freely suspended in liquid carrier solutions. However, it has become apparent that these methods result in poor cell retention and survival, thus reducing therapeutic potential. Naturally derived or synthetic materials have been explored to enhance stem cell survival and retention in vivo such as extracellular matrix (ECM)-based natural materials. In the present study, we employed porcine small intestinal submucosa (SIS), an ECM-based natural material, in conjunction with our BM-derived MSCs as an implantable device for tissue repair. The material is derived from SIS through a process where the ECM is decellularized while still retaining the naturally fibrous and porous nature of the matrix as well as several matrix-associated cytokines. Currently, SIS ECM has been used in cardiac repair and pericardial closure in the clinic, but mainly for providing structural support. To maximize its regenerative capability, we propose to recellularize the SIS ECM with BM-derived MSCs, thereby combining the mechanical and biochemical properties of the SIS ECM with the therapeutic capabilities of the MSCs. The goal of this study was to assess the angiogenic secretome changes of the combined SIS ECM and MSC product when compared to SIS ECM or MSCs alone. In this study, we investigated secretome changes of MSCs after culture on SIS ECM for up to 72 hours. We then focused on two key angiogenic factors, VEGF-A and IL-8, and analyzed their release as a function of time as well as donor origin. Finally, we confirmed the functional relevance of these secreted cytokines in promoting cardiac endothelial cell tube formation.

**Scientific Abstract:**
INTRODUCTION: The in vivo therapeutic effect of mesenchymal stromal cells (MSCs) is currently believed to be tightly linked to their paracrine secretion ability. However, insufficient or imprecise cell delivery, low cell survival and retention post-transplant, along with harsh donor site microenvironments, are major barriers to the clinical success of MSC therapies. Here we tested a small intestinal submucosa (SIS)-derived extracellular matrix (ECM) bioscaffold augmented with MSCs, with the hypothesis that they will facilitate the precise delivery of increased numbers of MSCs therefore improving cell viability and retention. METHODS: In this study, we evaluated the secretion of angiogenic factors from three human MSC lines cultured on SIS ECM. We used human antibody array and enzyme-linked immunosorbent assay to measure the level of angiogenic factors released from MSCs when cultured on SIS ECM or regular tissue culture plastic. We tested MSCs cultured for three different time points. RESULTS: We found that the SIS ECM culture environment can significantly enhance the release of several angiogenic factors when compared to MSCs cultured on standard tissue culture plastic. Specifically, vascular endothelial growth factor and interleukin-8 secretion was significantly increased at 24, 48 and 72

hours postseeding onto SIS ECM whereas vascular endothelial growth factor release for cells cultured on plastic surface remained the same during these time points. We also observed significant donor to donor variation in cytokine production. CONCLUSIONS: This study demonstrates that MSCs transplanted onto a SIS ECM may greatly increase their therapeutic potential through an increase in pro-angiogenic cytokine release.

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